REMARKS

This is in full and timely response to the above-identified Office Action. The above listing of the claims supersedes any previous listing. Favorable reexamination and reconsideration are respectfully requested in view of the preceding amendments and the following remarks.

Claim amendments

In this response, claim 15 has been amended in a manner to obviate a minor typographical error and to improve syntax. The scope of the claim is completely unchanged and thus entry of the amendment is deemed proper.

Rejections under 35 USC §103

The rejection of claims 1-2, 4-9, 12-19 and 21 under 35 USC § 103(a) as being unpatentable over Wong et al. (US patent 5,935,793) in view of the article to Heath et al. is again respectfully traversed.

In order to establish a *prima facie* case of obviousness, it is necessary to show that the hypothetical person of ordinary skill would, without any knowledge of the claimed subject matter and without any inventive activity, be provided with disclosure of all of the claimed elements and then be able to arrive at the claimed subject matter given the guidance of the cited references when each is fully considered as statutorily required.

Firstly, it is submitted that the hypothetical person of ordinary skill would not combine these documents. As a result a *prima facie* case of obviousness cannot be established.

Indeed, contrary to the opinion of the Examiner, the method taught by Wong is not at all similar to the method of Heath. The Examiner argues that both methods share a universal primer site as well as an intermediate region (tag sequence). The mere fact,

however, that two methods share one or more isolated features is totally insufficient to conclude that these methods are in fact similar to the degree that teachings could be transferred therebetween.

Universal primer sequences and tag sequences as such are used in numerous DNA-based methods, and these methods mostly do not have any similarity with either the method of Wong or Heath. This is because these features do not necessarily serve the same purpose in different methods. Indeed, when arguing a similarity between methods which share a common feature, one must not disregard the specific context in which a feature occurs within a given process.

For example, Wong and Heath make use of a universal primer sequence for completely different reasons. In the method of Wong, the universal primer sequence (designated 44 in Fig. 15) is used as a starting point for a primer extension reaction. It hybridizes with its complementary sequence in a cloning vector harboring the sample fragments to be sequenced, and the cloning vector is used as a template for the primer extension reaction (see column 12, lines 39-56). The primer extension reaction is performed according to the chain termination method of Sanger, which means that primer extension is carried out in the presence of one of the dideoxynucleotides ddATP, ddGTP, ddCTP, or ddTTP.

Incorporation of a dideoxynucleotide into the growing DNA strand synthesized in the primer extension reaction terminates DNA strand extension and results in a mixture of DNA fragments of varying lengths (the -sequencing fragments"). In other words, the universal primer sequence is used in Wong as a tool for generating a high number of different sequencing fragments without the necessity of synthesizing a specific primer for each of the different sample fragments.

In contrast, Heath uses the universal primer sequences to

amplify a number of different PCR products which have been obtained from a first PCR reaction using several specific primers. Each of these specific primers is tagged with a universal primer sequence. By introducing universal primer sequences it is then possible to amplify all target molecules in a second reaction without any disturbance caused by the concurrent use of a high number of different primer sequences (see Fig. 1 at page 274). In the method of Heath, the universal primer sequences are used in the form of a primer pair for PCR amplification.

It follows that although the teachings of Wong and Heath both use one or more universal primer sequences, this does not at all render them similar in eyes of the hypothetical person of ordinary skill.

The tag sequence is also not a feature which renders the methods of Wong and Heath similar. In Wong, the tag sequence is used to allow for the identification of a sequencing fragment which corresponds to a particular sample fragment (see column 3, lines 43-48). Such an identification function cannot be ascribed to the tag sequence discussed in Heath. At page 274, left column, it is outlined that the "tag" sequence of the primers used in the first PCR reaction consists of 6 nucleotides and is exclusively used for DNA sequencing. This means that the tag sequence of Heath does not differ between the different PCR products, but instead provides a universal primer site to which a sequencing primer can hybridize. Thus, Heath does not make use of the tag sequence for identifying a certain group of nucleic acid molecules. In fact, Heath does not disclose or suggest any kind of identification means which would be based on a unique sequence tag.

Hence, this feature is also not suitable for arguing similarity between the methods of Wong and Heath.

For the above reasons, the hypothetical person of ordinary skill would not have combined the prior art documents of Wong and

Heath when trying to solve the problem underlying the present invention.

Moreover, it is submitted that even if the hypothetical person of ordinary skill would consider combining the teachings of Wong and Heath, such combination would not lead a person to the claimed invention. The Examiner argued that the skilled person would have been motivated to apply the teaching of Heath to the method of parallel sequencing taught by Wong (see page 12 of the office action, end of the 1st para.). However, given the rationale of the method of Wong which is clearly based on a primer extension reaction using a single primer to generate sequencing fragments, it remains completely unclear how one could use the teachings of Heath with the sequencing method of Wong. The Examiner states in this respect at page 9, third paragraph, that Wong describes the first step of the method as requiring at least one primer for the extension of the original sample sequence. It is stated by the Examiner that this teaching could also encompass PCR amplification (see page 9 of the office action, 3rd para.). This is, however, not correct.

The method of Wong is based on a single primer extension reaction for generating dideoxynucleotide-terminated sequencing fragments. It would make no sense at all to modify the first step of Wong in a manner to include a second primer extension reaction in which the first primer extension products serve as a template for the generation of a second primer extension product, as required by the claimed method. To achieve such modification, one would have to abstain from using dideoxynucleotides in the primer extension re-action, so that a full-length first primer extension product can be amplified. This, however, would countervail the actual purpose of the first step, namely the generation of sequencing fragments of different lengths.

At page 24, last paragraph, the Examiner furthermore states

that it would have been *prima facie* obvious to incorporate the primer format taught by Wong into a method of PCR amplification. Applicant respectfully disagrees. When looking at the structure of the primers used in Wong, it is to be noted that the primers share a 3'-universal sequence (which is designated 26 in figure 1A and 44 in figure 1B, respectively) and a unique tag sequence. Binding of the primers to their target sites in the cloning vectors is accomplished via their 3'-universal sequence, and the primers are subsequently extended in the direction from 5' to 3'.

It is therefore submitted that that such a primer design would be useless in a method as claimed by the present invention. Reference is made in this regard to figure 2 of the present application which explains the general structure of the primers P1 and P2 according to the invention. It is directly apparent that the 3'-ends of these primers are target-specific primers which are based on the specific sequence of the target nucleic acid to be amplified. The use of a primer having a 3'-universal sequence in the method of the present invention would not lead to desired results.

At page 25, the Examiner also argues that Wong would teach method step d) of claim 1 which requires a second primer pair that selectively hybridizes to the constituent segments C1 and C3, respectively. The Examiner states that the primers of Wong hybridize to these respective elements in the primer-tag-primer of Fig. 1B (see page 25, end of 2nd para...) However, it is submitted that it is not possible to equate the primer-tag-primer of figure 1B in Wong with the constituent segments C1 and C3 as defined in the claims of the present application.

The constituent segments C1 and C3 refer to regions within two different primers of the first primer pair, whereas the "corresponding" regions in Wong are located in a single primer. For at least this reason, the comparison drawn by the Examiner is

flawed. If at all, the region of primer P2 which corresponds most to the region designated 44 in Wong, is constituent segment C4. However, in the method contemplated in this application, it is senseless to amplify the tag sequence with primers hybridizing to the C3 and C4 regions. Such amplification would completely fail to lead the hypothetical person of ordinary skill to the claimed subject matter.

Other cited references do not rectify the deficiencies of Heath and Wong.

Conclusion

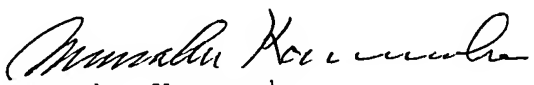
In conclusion, none of the publications of Heath or Wong is able to render obvious the subject-matter of present claim 1. Therefore, claim 1 as it stands before the PTO, is clearly non-obvious in light of the art which is applied. Dependent claims 2-37 are non-obvious and allowable over the cited art for at least the same reasons that claim 1 is so allowable.

It is respectfully submitted that the claims as they have been amended are therefore allowable over the art which has been applied in this Office Action.

Favorable reconsideration and allowance of this application are courteously solicited.

A one month extension of time is hereby requested. A credit card authorization form in the amount of $130.00 is attached herewith for the three month extension of time.

Respectfully submitted,



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